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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,503	02/21/2001	Samuel J. Tremont	2045.40PCT/US	7558

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EXAMINER	
ZALUKAEVA, TATYANA	
ART UNIT	**PAPER NUMBER**
1713	9

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

MK-8

Office Action Summary	Application No.	Applicant(s)	
	09/647,503	TREMONT, SAMUEL J.	
	Examiner	Art Unit	
	Tatyana Zalukaeva	1713	

-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 15 is rejected under 35 U.S.C. 102(b) as anticipated by Ebert et.al. (Journal of Biomedical materials Research, Vol.16, 629-638, 1982) or Blossey et.al (J.Org Chemistry, 1990, 55,4664-4668). Or Sarobe et.al. (Polymers for Advanced Technologies, Volume 7, 749-753, 1996), or Severian et al (Reaserch Paper "Bioactive Polymers" 58 Chim OGGI, 09-1988, No.9, 59-63), each one individually.

Ebert et.al. describe the immobilization of **prostacyclin (active ingredient)** on **a polymer** surface to ensure its sustained release over time. The procedure involves the use of **diaminoalkane spacer (linker) arm interposed between the polymer surface and immobilized active ingredient.** (page 630, 3-d paragraph).

In Materials and Methods section Ebert exemplifies a polymer chosen for immobilization as crosslinked polystyrene beds, which were further chlorsulfonated. The spacer was linked to preliminary prepared polymer , wherein the bonding between linker and polymer was confirmed by UV-Spectral analysis. After this stage was accomplished, the

active ingredient, namely prostaglandin F2-alpha, was contacted with derivatized polymer to produce an immobilized (covalently bonded) physiologically active compound. The immobilized preparation showed improved release of an active ingredient versus time. The release of the said active ingredient which hag platelet aggregation inhibiting properties was due to its biodegradation (hydrolysis) of a covalent bond between the active ingredient and linker.

Blossey discloses drug delivery system wherein **dehydrocholic and cholic acid (active ingredient), attached via their carboxy group**, to chlormethylated polystyrene. Synthetic transformation of bound steroids containing carboxyl and hydroxyl groups and esterification of hydroxyl was confirmed by ^{13}C NMR. A spacer, p-alkoxybenzoyl group, was used in conjunction with crosslinked polystyrene support and hydrochloic acid to obtain sustained-release preparation of hydrocholic acid. The NMR spectrum showd strong ssignals, characteristic of cross-linked polystyrene, containing hydroxymethyl groups. (Page 4664, col.2).

Experimental Section of the article provides specifics for chlomethylated crosslinked polystyrene, and spacer (Merrifield peptide resin), namely p-alkoxybenzyl (p.4667, col.1).On page 4668 Blossey exemplifies the delivery system which consists of polymer-spacer-dehydrocholate, which means it contains an active ingredient containing carboxyl functional group, a linker which is attached to an active ingredient via hydrolyzable covalent bond and a crosslinked polymer. In the instant case the bond between the linker and polymer is an oxygen-carbon double bond.

Sarobe teaches systems comprising an immunoglobulin G (active ingredient, **protein having carboxyl and amino groups**), covalently coupled to chloromethylstyrene beads. One of the best known in the art procedures for coupling of amino groups of protein to a polymer is via a reaction of the said protein with water soluble carbodiimide (linker). Sarobe utilizes polystyrene beads with chloromethyl functional groups, prepared by **covalent coupling of polystyrenes** (polymer) with chloromethyl containing moieties (linkers) , and thus afterwards providing a one-step reaction of chloromethyl group of derivatized polymer with amino group of protein molecules. (Page 749, col.2) In the systems prepared with chloromethyl functionality, the attack of amino groups (in active ingredient molecule) on the chloromethyl groups of a polymer is governed by the diffusion of nucleophile.

Severein discloses drug delivery systems. Scheme 1 on page 63 provides for a delivery system, wherein a metronidazole (an active ingredient) is bonded covalently to a copolymer of acrylic acid with styrene via an activator dicyclohexyl carbodiimide.

Claim Rejections - 35 USC § 103

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Ebert et.al. (Journal of Biomedical materials Research, Vol.16, 629-638, 1982) or Blossey et.al (J.Org Chemistry, 1990, 55,4664-4668). Or Sarobe et.al. (Polymers for Advanced Technologies, Volume 7, 749-753, 1996), or Severian et al (Reaserch Paper "Bioactive Polymers" 58 Chim OGGI, 09-1988, No.9, 59-63), in view of Tremont et al (U.S. 5,827,925).

Although all cited references teach the covalent bonding of a linker, containing chloromethyl moieties to a polymer of polystyrene group, they do not explicitly exemplify the use of poly [(4-dimethylaminomethyl) styrene] as a polymer chosen as a matrix for drug delivery system.

Tremont discloses a drug delivery system which comprises one of prostaglandins as an active ingredient, which have active hydroxyl groups, ester groups keto-enol groups; (see abstract and column 3, lines 50-65, column 4, lines 1-60). Next constituent of a delivery system may be a polymeric material attached to a linker group. IN this case the covalent bond is formed between an active ingredient and a linker group and a linker group in its pwn turn is attached to a polymer. (col. 5, lines 40-47, col. 6, lines 55-65, scheme 1, col.9, line 15, column 10, lines 5-15). Polymers preferred by Tremont contain dimethylaminogroups . (see scheme 3 in col. 9 and 10).

Therefore a person skilled in the art would have found it obvious at the time the invention was made that polymers containing dimethylaminogroups , such as those of Tremont, useful for identical purpose and mage by identical prcess, as those of the four cited references, would be operable within the scope of Ebert , Blossey , Sarobe or Severian with the reasonable expectation of success, since the N-C bond, as well as S-C bond, as well as P-C bond formation requires less energy than C-O bond formation.

6. Applicants' Paper No. 7 states that claims 15-20 are presented for consideration. However, claim 29 **has not been** presented by Applicants. Therefore, claims 15-19 have been examined on the merits.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Royer (U.S. 5,783,214) discloses synthetic drug delivery system, comprising active ingredient, polymeric matrix and crosslinker; Hale et.al.

(U.S.5,607,691) disclose a method of delivering pharmaceutical agents, which are covalently bonded to a chemical modifier, via a physiologically cleavable bond; Tremont et.al. (U.S. 5,827,925) disclose a drug delivery system releasing an effective amount of drug within a specific range of pH values, the said system comprising a polymeric material and a drug covalently bonded to it via pH sensitive covalent bond; Yatvin et.al. (U.S. 5,480,674) disclose systems for specific site-directed delivery of pharmaceutical preparations, such as antimicrobial drugs covalently linked to particular carriers.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tatyana Zalukaeva whose telephone number is (703) 308-8819. The examiner can normally be reached on 9:00 - 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Wu can be reached on (703) 308-2450. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0651.

TATYANA ZALUKAEVA
PATENT EXAMINER

September 4, 2002

Tatyana Zalukaeva
Examiner
Art Unit 1713